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EXAMINER	
COLLINS, CYNTHIA E	
ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 02/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/851,084	BRISSON ET AL.	
	Examiner	Art Unit	
	Cynthia Collins	1638	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *7-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-6, in Paper No. 3 is acknowledged.

The traversal is on the ground(s) that it would not be serious burden on the Examiner to consider all the claims simultaneously (reply pages 2-3). The traversal is also on the ground(s) that there is unity of invention (reply page 3). Additionally, the traversal is on the ground(s) that the restriction requirement fails to clearly state why the inventions are independent and distinct (reply page 4).

This is not found persuasive because while the search of the different groups of invention may overlap insofar as they relate to the use of protein fragment complementation assays, their searches are not coextensive of each other. Each group of invention additionally requires a search for a product or methods not claimed in the other groups. With respect to the assertion that there is unity of invention, the Examiner maintains that the assertion is not relevant to the instant restriction requirement, as the unity of invention standard applies only to restriction of US applications filed under 35 USC 371. With respect to the assertion that the restriction requirement failed to clearly state why the inventions are independent and distinct, the Examiner maintains that specific reasons for why the inventions are independent and distinct were set forth at pages 4-5 of the restriction requirement mailed December 6, 2002. Accordingly, claims 7-26 are withdrawn from consideration as being directed to nonelected inventions.

The requirement is still deemed proper and is therefore made FINAL.

Specification

The specification is objected to because the abstract does not meet proper language format. Specifically, the form and legal phraseology used in patent claims, "said", is included. Applicant is reminded of the proper language and format for an abstract of the disclosure. The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details. The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The disclosure is also objected to because of the following informalities: reference to a provisional application under 35 USC 119(e) is not mentioned in the first paragraph of the specification. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a method of expressing PCA interacting partners in plant material comprising (A) transforming said material with (1) a first construct coding for a first fusion product comprising (a) a first fragment of any first molecule of any type from any source whose fragments can exhibit a detectable activity when associated and (b) a first protein-protein interacting domain; and (2) a second construct coding for a second fusion product comprising (a) any second fragment of said first molecule and (b) a second protein-protein interacting domain that can bind (1)(b); culturing said material under conditions allowing expression of said PCA interacting partners, and (C) detecting said activity.

The specification describes a method comprising (A) transforming plant material with (1) a first construct coding for a first fusion product comprising (a) a first fragment of a murine dihydrofolate reductase enzyme divided into two fragments whose two fragments can exhibit a detectable enzymatic activity when associated with each other and (b) a first protein-protein interacting domain; and (2) a second construct coding for a second fusion product comprising (a) the second fragment of said enzyme and (b) a second protein-protein interacting domain that can bind (1)(b); culturing said material under conditions allowing expression of said PCA interacting partners, and (C) detecting said enzymatic activity (pages 13-21). The specification does not describe or characterize any molecule other than a murine dihydrofolate reductase enzyme whose

fragments can exhibit a detectable activity when associated with each other in the context of a protein fragment complementation assay.

The Federal Circuit has recently clarified the application of the written description requirement. The court stated that a written description of an invention "requires a precise definition, such as by structure, formula [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lily and Co., 119 F.3d 1559, 1568; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The court also concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id. Further, the court held that to adequately describe a claimed genus, Patent Owner must describe a representative number of the species of the claimed genus, and that one of skill in the art should be able to "visualize or recognize the identity of the members of the genus." Id.

Given the claim breadth and lack of guidance as discussed above, the specification fails to provide an adequate written description of the genus as broadly claimed. Given the lack of written description of the claimed products, any method of using them would also be inadequately described. Accordingly, one skilled in the art would not have recognized Applicants to have been in possession of the claimed invention at the time of filing. See Written Description Requirement guidelines published in Federal Register/ Vol. 66, No.4/ Friday January 5, 2001/Notices: pp. 1099-1111).

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of expressing protein fragment complementation assay

interacting partners in plant material comprising (A) transforming plant material with (1) a first construct coding for a first fusion product comprising (a) a first fragment of a murine dihydrofolate reductase enzyme divided into two fragments whose two fragments can exhibit a detectable enzymatic activity when associated with each other and (b) a first protein-protein interacting domain; and (2) a second construct coding for a second fusion product comprising (a) the second fragment of said enzyme and (b) a second protein-protein interacting domain that can bind (1)(b); culturing said material in the presence of fluorescent substrate and under conditions allowing expression of said PCA interacting partners, and (C) detecting said enzymatic activity by fluorescence microscopy, spectrofluorometry, FACS analysis or a fluorescence-detecting video system, including methods in which the interaction of said protein-protein interaction domains is facilitated by the addition during culturing of an inducer that specifically induces the binding of said protein-protein interaction domains, does not reasonably provide enablement for other methods of expressing protein complementation assay interacting partners in plant material that utilize other types of first molecules. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn to a method of expressing PCA interacting partners in plant material comprising (A) transforming said material with (1) a first construct coding for a first fusion product comprising (a) a first fragment of any first molecule of any type from any source whose fragments can exhibit a detectable activity when associated and (b) a first protein-protein interacting domain; and (2) a second construct coding for a second fusion product comprising (a) any second fragment of said first molecule and (b) a second protein-protein interacting domain

that can bind (1)(b); culturing said material under conditions allowing expression of said PCA interacting partners, and (C) detecting said activity, including methods in which any type of inducer is added to facilitate the interaction of said protein-protein interaction domains.

The specification discloses a method of expressing protein fragment complementation assay interacting partners comprising (A) transforming potato or tobacco leaf protoplasts with (1) a first construct coding for a first fusion product comprising (a) a first fragment of a murine dihydrofolate reductase enzyme divided into two fragments whose two fragments can exhibit a detectable enzymatic activity when associated with each other and (b) a first protein-protein interacting domain, exemplified by GCN4, NPR-1/NIM1 or FKBP respectively; and (2) a second construct coding for a second fusion product comprising (a) the second fragment of said enzyme and (b) a second protein-protein interacting domain that can bind (1)(b), exemplified by GCN4, TGA2 or FRB respectively, culturing said material in the presence of fluorescein-conjugated methotrexate substrate and under conditions allowing expression of said PCA interacting partners, and (C) detecting said enzymatic activity by fluorescence microscopy, spectrofluorometry or FACS analysis (pages 13-21). The specification also discloses a method in which the inducer rapamycin is added during culturing to facilitate the binding of FKBP and FRB protein-protein interacting domains to each other (page 18), and a method in which the inducer salicylic acid is added during culturing to facilitate the binding of NPR-1/NIM1 and TGA2 protein-protein interacting domains to each other (pages 19-21). The specification does not disclose methods using any molecule other than a murine dihydrofolate reductase enzyme whose fragments can exhibit a detectable activity when associated with each other in the context of a protein fragment complementation assay.

Guidance for making and using the claimed invention is necessary because the ability of molecular fragments to exhibit a detectable activity when associated with each other in the context of a protein fragment complementation assay is unpredictable. For example, Michnick et al. (Methods in Enzymology, 2000, Vol. 328, pages 208-230) teach that enzymes used for protein fragment complementation assays must be dissected into fragments that are subdomains of the complete protein yet not capable of spontaneously folding into complete functional proteins (page 213). Michnick et al. also set forth specific criteria for identifying those enzymes that may be useful (page 213). Michnick et al. additionally teach that the optimal site of cleavage for a particular enzyme is limited by its specific structural and functional constraints, and the manner in which an enzyme fragment is fused to a protein-protein interacting domain is also a constraint on experimental design (page 215). In the instant case, Applicant has provided guidance only for the use of murine dihydrofolate reductase as the molecule whose fragments can exhibit a detectable activity when associated with each other in the context of a protein fragment complementation assay. Applicant provides no guidance with respect to the identity and preparation of other molecules that could substitute for murine dihydrofolate reductase.

Given the claim breadth, unpredictability, and lack of guidance as discussed above, it would require undue experimentation for one skilled in the art to determine which nonexemplified molecules to use and how to prepare them such that their fragments would exhibit a detectable activity when associated with each other in the context of a protein fragment complementation assay.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4 and 5, and claims dependent thereon, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in the recitation of "PCA interacting partners". The meaning of the acronym "PCA" is unclear. It is also unclear what constitutes a "partner". Additionally, the nature of the interaction between the partners is unclear.

Claim 1 is indefinite in the recitation of "a first molecule whose fragments can exhibit a detectable activity when associated". It is unclear which fragments of the first molecule exhibit a detectable activity when associated; all of the possible fragments of the first molecule associated in any combination? Only specific fragments in specific combinations?

Claim 1 is indefinite in the recitation of "a detectable activity". The nature of the activity to be detected is unclear.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Part (C) of claim 1 requires detecting an activity, but the claim recites no steps by which this may be accomplished.

Claim 4 is indefinite in the recitation of "where an inducer is added to facilitate the interaction of said protein-protein interaction domains". It is unclear what is being induced by the inducer. It is also unclear in what way the interaction of the protein-protein interaction domains is being facilitated. Additionally, it is unclear at what step of the method an inducer would be added in order to achieve the desired results.

Claim 4 is indefinite in the recitation of "the interaction of said protein-protein interaction domains". There is insufficient antecedent basis in claim 1 for the limitation "the interaction of said protein-protein interaction domains" in claim 4, as claim 1 does not require the interaction of protein-protein interaction domains.

Claim 5 is indefinite as it is unclear at what step of the method a fluorescent substrate would be added in order to achieve the desired results. It is also unclear what the fluorescent substrate is a substrate for.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gutterson et al. (Patent No. US 6,392,119, effective filing date January 24, 1997) in view of Pelletier et al. (Proc. Natl. Acad. Sci. USA, October 1998, Vol. 95, pages 12141-12146) and Remy et al. (Science, February 1999, Vol. 283, pages 990-993), and further in view of Chang et al. (Patent No. US 5,610,042, issued March 11, 1997).

The claims are drawn to a method of expressing PCA interacting partners in plant material comprising (A) transforming said material with (1) a first construct coding for a first fusion product comprising (a) a first fragment of a first molecule whose fragments can exhibit a detectable activity when associated and (b) a first protein-protein interacting domain; and (2) a

second construct coding for a second fusion product comprising (a) a second fragment of said first molecule and (b) a second protein-protein interacting domain that can bind (1)(b); culturing said material under conditions allowing expression of said PCA interacting partners, and (C) detecting said activity by fluorescence microscopy, spectrofluorometry, FACS analysis or a fluorescence-detecting video system, including methods in which an inducer is added to facilitate the interaction of said protein-protein interaction domains.

Gutterson et al. teach a method of expressing bacterial barnase enzyme fragments in plant material comprising (A) transforming said material with (1) a first construct coding for a first polypeptide product comprising (a) a first fragment of a barnase enzyme whose fragments can exhibit a detectable activity when associated, and (2) a second construct coding for a second polypeptide product comprising (a) a second fragment of said barnase enzyme; culturing said material under conditions allowing expression of said barnase interacting partners, and (C) detecting barnase activity by measuring its effect on luciferase activity (column 28 line 15 through column 30 line 20).

Gutterson et al. do not teach methods comprising transforming plant material with constructs coding for fusion products between protein-protein interacting domains and molecules whose fragments can exhibit a detectable activity when associated, or detection of an activity by detecting said activity by fluorescence microscopy, spectrofluorometry, FACS analysis or a fluorescence-detecting video system, or methods in which an inducer is added to facilitate the interaction of protein-protein interaction domains.

Pelletier et al. teach a method of expressing PCA interacting partners in bacteria comprising (A) transforming bacteria with (1) a first construct coding for a first fusion product

comprising (a) a first fragment of murine dihydrofolate reductase and (b) a first yeast GCN4 protein-protein interacting domain; and (2) a second construct coding for a second fusion product comprising (a) a second fragment of murine dihydrofolate reductase and (b) a second yeast GCN4 protein-protein interacting domain that can bind (1)(b); culturing said material under conditions allowing expression of said PCA interacting partners, and (C) detecting said activity by fluorimetry (pages 12142-1243).

Remy et al. teach methods of expressing PCA interacting partners in mammalian cells comprising (A) transforming mammalian cells with (1) a first construct coding for a first fusion product comprising (a) a first fragment of murine dihydrofolate reductase and (b) a first EpoR or JAK2 protein-protein interacting domain; and (2) a second construct coding for a second fusion product comprising (a) a second fragment of murine dihydrofolate reductase and (b) a second EpoR or JAK2 protein-protein interacting domain that can bind (1)(b); culturing said cells in the presence of fluorescein-conjugated methotrexate substrate and under conditions allowing expression of said PCA interacting partners, and (C) detecting said activity by FACS analysis and fluoresecence microscopy, including methods in which Epo or JAK2 induces the interaction of said protein-protein interaction domains (page 991 Figures 1 and 2, page 992 Figure 3).

Chang et al. teach the expression of enzymatically active dihydrofolate reductase, including murine dihydrofolate reductase, in plant cells and selection of plant cells using methotrexate (column 5 lines 10-17; column 14 claims 1-5).

Given the success of Gutterson et al. in expressing heterologous enzyme fragments in plant cells such that enzymatic activity was reconstituted, and given the success of Pelletier et al. and Remy et al. in expressing fusion products between protein-protein interacting domains and

dihydrofolate reductase enzyme fragments in bacterial and mammalian cells such that enzymatic activity was reconstituted, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to transform plant cells as taught by Gutterson et al. with constructs coding for fusion products between protein-protein interacting domains and enzyme fragments such as those taught by Pelletier et al. and Remy et al., given the express purpose of expressing such fusion products in plant material, and given that expression of enzymatically active dihydrofolate reductase in plants was known at the time of Applicant's invention, without any surprising or unexpected results. Accordingly, one skilled in the art would have been motivated to generate the claimed invention with a reasonable expectation of success. Thus, the claimed invention would have been *prima facie* obvious as a whole to one of ordinary skill in the art at the time the invention was made.

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia Collins whose telephone number is (703) 605-1210. The examiner can normally be reached on Monday-Friday 8:45 AM -5:15 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

CC
February 21, 2003

DAVID T. FOX
PRIMARY EXAMINER
GROUP ~~180~~ 1638